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Abstracts

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Pathogenesis of hypertension associated with chronic kidney disease without overt renal failure. *C. Beretta-Piccoli, P. Weidmann, R. de Chatel and F. C. Reubi. Policlinique de Médecine, Université de Berne, Switzerland.* Interrelations among blood pressure, exchangeable sodium, blood volume and plasma renin activity were studied in 40 normal subjects and 40 patients with chronic kidney disease and a mean plasma creatinine concentration of 2 mg/100 ml. Findings in eight normotensive patients did not differ from those in normal subjects. However, 32 hypertensive patients showed increases ($P < 0.05$) in exchangeable sodium and in the products of the logarithm of plasma renin activity and exchangeable sodium or blood volume. In the patients with renal disease, blood pressure correlated significantly ($P < 0.05$) with duration of hypertension ($r = 0.70$), exchangeable sodium ($r = 0.34$) and with the exchangeable sodium-renin ($r = 0.38$) or blood volume-renin ($r = 0.30$) products; but not with blood volume or circulating renin individually. It correlated inversely with the glomerular filtration rate ($r = -0.33$) and the para-aminohippurate (PAH) clearance ($r = -0.41$). These findings suggest that hypertension accompanying kidney disease without overt renal failure may depend partly on abnormalities in the sodium/volume-renin feedback mechanism as well as a factor related to the duration of preexisting hypertension, and possibly to the grade of renal vascular changes.

***De novo* membranous glomerulonephritis in two renal allografts.** *P. Collin, J. P. Saint-Andre, M. C. Gubler, R. Spiesser and P. Riberi. Service de Nephrologie et Laboratoire d'Anatomie Pathologique, C.H.U. Angers, Cedex, France.* A 35-year-old white woman and a 10-yr-old boy with focal sclerosing glomerulonephritis, who developed chronic renal failure, received cadaver renal allografts. Four months later, massive, persistent proteinuria developed. The renal tissue of homograft showed characteristic changes of membranous glomerulonephritis. The criteria for *de novo* membranous glomerulonephritis in renal allografts are met in these cases. In the first case, the loss of renal function at the 19th month is suggestive of chronic rejection of the renal allograft. In the second case, the development of a membranous lesion in the transplanted kidney secondary to the presence of hepatitis HB Ag cannot be excluded.

Brush border membrane fragments of the proximal tubule in human urine. *M. E. De Broe, F. Roels, S. Ringoir and R. J. Wieme. Departments of Nephrology, Anatomy, and Clinical Chemistry, State University, Ghent, Belgium.* Recently we adduced clinical, biochemical and morphological evidence for the release of plasma membrane fragments (PMF) into the circulation of patients with cholestasis (De Broe ME, Weime RJ: *Clin Chim Acta* 59:369; 1975). Human urine was investigated in view of the fact that the proximal tubule of the kidney, involved in transport process, could be the source of a similar plasma membrane shedding. Urine of normal subjects and of patients at onset of diuresis after acute oligo-anuric renal failure was investigated. Proximal tubule brush border enzymes (alkaline phosphatase, γ-glutamyl-transferase, 5'-nucleotidase, leucinaminopeptidase, maltase) were found to occur in a macromolecular form which we had designated by the term "koinozymes" referring to different enzymes occurring on a single kinetic unit (Weime RJ, De Broe ME: *Clin Chem* 21:956, 1975). This was shown by electrophoresis in different media and chromatography using Sepharose 4B. The density of these isolated koinozymes was 1.205 determined after 24 hr of ultracentrifugation in a 20, 25 or 30% CsCl gradient. The sodium dodecylsulfate polyacrylamide gel electrophoretic pattern of the isolated koinozymes demonstrates several polypeptide chains (mol wt: > 300,000 to 22,000). Lipid extraction followed by thin-layer chromatography revealed cholesterol, free and esterified, and several types of phospholipids. Electron microscopy of the macromolecular fractions shows multiple vesicles bounded by a triple-layered membrane of variable size, where the enzyme reaction product (alkaline phosphatase) is contiguous to the outer surface of the membrane. This result fits well with our earlier observations in the serum of patients with cholestasis and recently in duodenal fluid and the supernatant of cultured HeLa cells and lymphocytes. The significance of this PMF release in the human urine remains to be elucidated.

Physiological determinants of angiotensin II pressor responsiveness in normal subjects and in patients with terminal renal failure. *J. Deheneffe, V. Cuesta, J. D. Briggs, J. J. Brown, A. F. Lever, J. J. Morton, W. Oelkers and J. I. S. Robertson. Department of Internal Medicine, University of Liège, Liège, Belgium and MRC Blood Pressure Unit, Western Infirmary, Glasgow, Scotland.* Incremental angiotensin II (A II) infusions were performed at doses of 2, 4, 8 and in some cases 12 ng · kg^{-1} · min^{-1} for one hour each in ten normal volunteers and in ten patients with terminal renal failure (six anephrics). In five normal subjects, they were repeated after three days of dietary Na depletion (10 to 15 mEq/24 hr) combined with i.v. administration of 40 mg of frusemide, whereas all patients with renal failure had a new infusion after three days of dietary Na restriction combined with weight-reducing hemodialysis. When the log of plasma A II concentrations was plotted against the corresponding increases in diastolic blood pressure (DBP), there was a shift to the right of the dose-response curves in the normal subjects and in the "nephric" patients after Na depletion. Conversely, no such phenomenon was observed in the anephrics, whose basal A II levels were unchanged by Na depletion. In all cases, a direct correlation was found between basal A II and the pressor threshold. When increases in plasma A II concentration were plotted against the corresponding rises in DBP, there was an inverse correlation between the log of basal A II concentrations and the slopes of the pressor A II dose-response curves. This relationship was not significantly altered when the normal subjects only or the patients with renal failure only were considered. No relationship could be found between basal DBP and the corresponding slopes of the A II pressor curves. The results suggest that (*1*) in anephric subjects pressor responsiveness is not altered by isolated Na depletion (no increase in A II concentration); (*2*) the inverse relationship between basal A II concentrations and the slopes of the pressor dose-response curves to A II is not altered by chronic renal insufficiency; (*3*) basal DBP is not a physiological determinant of pressor responsiveness to A II.

Renal glycosuria and transplantation. *A. Hadj Aissa, N. Pozet, J. L. Touraine, M. V. Pellet and J. Traeger. Service d'Exploration Fonctionnelle Rénale, Clinique de Néphrologie et des Maladies Métaboliques, Hôpital E. Herriot, Lyon Cedex, France.* The pathogenesis

of renal glycosuria (RG) remains uncertain: specific tubular disease or prediabetic state. Transplantation of such a kidney is a unique opportunity to try to distinguish the anomaly of the kidney itself from a possible metabolic general perturbation. A 35-yr-old woman with end-stage chronic renal failure was successfully treated by kidney transplantation from a HL-A A, B and D identical sibling. The 26-yr-old male donor had satisfactory radiological and functional pretransplantation tests, aside from a slight obesity and intermittent glycosuria. A normal high dose per os glucose tolerance test (HPOGTT) with decreased minimal treshold (1.4 g/liter) and Tm glucose (172 mg/min/1.73 m^2) proved the existence of RG in the donor. This moderate RG did not seem to be a contraindication to the kidney removal for transplantation. After the transplantation, further investigations demonstrated no RG in the recipient (one month after transplantation TmG = 260 mg/min; two years after TmG = 150 mg/min; and three years after TmG = 209 mg/min/1.73 m^2) who had a normal renal function (one year after transplantation glomerular filtration rate = 65 ml/min, and three years after, GFR = 74 ml/min/1.73 m^2). In the donor, laboratory findings of RG disappeared, but distinct signs of diabetes mellitus were noted (HPOGTT and insulinemia). These results raise several questions concerning the pathogenesis of RG, the relations between RG and diabetes mellitus, the adaptation of tubular reabsorption of glucose to new conditions and the possible role of nephrectomy in revealing a latent diabetes mellitus.

Effects of clopamide and furosemide on the blood urea of rats with congenital diabetes insipidus. *J. L. Imbs, M. Schmidt, A. Parrenin, H. Belhadj-Mostefa and J. Schwartz. Inst. Pharmacologie. Fac. Méd. Strasbourg, France.* The increase in blood urea produced by diuretics is usually attributed to a reduction in extracellular fluid volume. In Brattleboro rats with congenital diabetes insipidus, diuretics increase natriuresis, but reduce polyuria. It is thus possible to study the action of diuretics on renal function in these animals without affecting water balance. We compared the effect of large doses (800 mg p.o.) of clopamide and furosemide. Blood urea (urease micromethod) increased in all the animals, but the increase was greater and more rapid with furosemide than with clopamide. Four hours after administration of the diuretics, the urine flow had dropped from 2.27 to 0.54 ml/100 g of rat/hr with furosemide and from 2.40 to 0.33 ml with clopamide, while the blood urea values were 32.8 ± 1.6 mg/100 ml of plasma and 18.2 ± 2.7 mg ($P < 0.001$), respectively. This greater increase in blood urea produced by furosemide in the rat with diabetes insipidus without loss of water would appear to be directly connected with its mode of action on the nephron. These results supplement those obtained with the Wistar rat with induced renal insufficiency (Imbs et al: *Thérapie* 30:125, 1975), in which furosemide (5 mg/kg) reduced the excretion of urea and creatinine in the urine more significantly than clopamide (16 mg/kg), with the same natruretic effects.

Nephrographic patterns after high dose urography in acute renal failure. *J. Joffre, D. Durand, J. L. Sablayrolles, J. Putois and J. M. Suc. Service de Nèphrologie, Groupe INSERM U-133 and Service de Radiologie, C.H.U. Rangueil, Toulouse, France.* Seventy-five patients presenting with acute renal failure were examined by i.v. urography according to the following method: a high dose of contrast medium (2 ml/kg) was quickly injected i.v. and early tomograms adapted with circulation transit time were performed. With this technique, a study of the vascularization and of the different nephrographic stages was obtained. The patients were divided into four groups: *1st group* (18 cases): obstructive acute renal failure: In 75% of these 18 patients, the diagnosis was made by the visualization of intrarenal lacunae on early tomograms. *2nd group* (7 cases): acute renal failure of vascular origin: In all cases, no cortical nephrography was noted. *3rd group* (42 cases): acute renal failure of parenchymatous origin: The urographic patterns were homogeneous: in about 85% of the cases, the early cortical nephrogram was good, and the late global nephrogram was dense and persisting. This pattern was noted as well in acute tubular necrosis as in acute glomerulonephritis. *4th group* (8 cases): acute transplant rejection: In 6 cases with severe acute rejection, the nephrogram was faint and persisting. These observations are important for diagnosis and subsequent investigations, and in some cases for establishing treatment.

Nonsystemic glomerular diseases and inhalation of organic solvents. *G. Lagrue, T. Kamalodine, J. Guerrero, F. Zhepova and J. Bernaudin. Department of Nephrology and INSERM U 139, Hôpital Henri-Mondor, Creteil, France.* The possible role of exposure to organic solvents and various inhaled toxic substances was studied in 108 cases of nonsystemic chronic glomerulonephritis. The frequency and intensity of exposure of the patients were compared to those of a matched control population. The degree of exposure was graded by a single investigator according to the method of Beirne (scale 1 to 10, *Lancet* 2:199-201, 1975). An exposure to inhaled toxic substances was found in 62% of the pathologic cases and in only 28% of the controls. The degree of exposure was significantly ($P < 0.005$) higher in the patient group (6.25 ± 2.47) than in the control group (3.90 ± 1.85). When the patients were classified according to histological findings, the frequency of exposure was similar in all groups. Industrial substances (hydrocarbon solvents chiefly, fuels and paints) were involved in most cases. These results suggest that inhalation of organic solvents and other inhaled substances may participate in the pathogenesis of glomerular diseases. The exact mechanism of this phenomenon remains unknown. A direct toxic effect seems unlikely. A more attractive hypothesis would be an alteration of the immune status of exposed patients.

Urinary excretion pattern of a pluridisperse protein solution. *M. Laurent and P. P. Lambert. Laboratory of Experimental Medicine, Brussels University and Queen Elisabeth Foundation, Brugmann Hospital, Brussels, Belgium.* A pluridisperse solution of proteins derived from gelatin (Haemacel, currently used as plasma expander) is separated by chromatography into two fractions (E. S. radii (a_s) of about 35 and 50 Å) which are iodinated and mixed (2:1 ratio). A total of 200 mCi of ^{125}I-labelled Haemacel are infused i.v. in Nembutal-anesthetized dogs during classical clearance experiments. The sieving coefficients (Φ) for each a_s are derived from the data of plasma and urine chromatography on Sephadex G 200. Mean maximum Φ (seven dogs) reached 0.240 (SEM, 0.070) for an a_s of 18.2 Å (SEM, 0.7), whereas Φ of 0.95 or greater is reached for the same a_s with PVP. Φ decrease with increasing a_s. Sieving restriction owing to electrical charge f.i. or tubular reabsorption may account for this difference. The latter is tested by trying to saturate it with an unlabelled Haemacel overload (four experiments). Φ maximum increased from 0.117 (SEM, 0.029) to 0.347 (SEM, 0.037) ($P < 0.001$). Unlabelled Haemacel overload does not equalize 18 Å Haemacel molecules and inulin clearances; thus, factors other than tubular reabsorption, perhaps electrical charges, restrict Haemacel urinary excretion.

Membranous glomerulonephritis (MGN) with extrarenal disorders in children. *C. Kleinknecht, M. Levy, M. F. Gagnadoux and R. Habib. Hôpital des Enfants-Malades, Paris, France.* Extrarenal disorders coexisted with nephropathy in 29 of 82 children with MGN. In 18 of these, the responsibility of a definite antigen (Ag) can be suspected: (*1*) hepatitis B Ag (HBAg) in 6 children; 3 of them presented with acute hepatitis and recovered from their nephropathy despite the persistence of HBAg; (*2*) systemic lupus erythematosus (2 cases); (*3*) sickle cell disease (1 case) or trait (3 cases); (*4*) congenital syphilis in one infant who recovered after penicillin therapy; (*5*) penicillamine therapy for Wilson's disease (1 case); (6) a streptococcal hypersensitivity suspected in 4 patients who presented with scarlet fever (3 cases) or rheumatic fever (1 case). The associated findings in the 11 remaining patients suggested a multiorgan involvement due to circulating immune complexes of unknown origin: thrombopenic purpura (1 case); arthralgias, myalgias, fever and purpura coexisting with the onset of MGN, five years after remission of a myelomonocytic leukemia (1 case); proximal tubular dysfunction (2 cases) with presence of antitubular and antilung basement membrane antibodies in the child who underwent immunopathologic investigations; polyarthralgias with or without fever, and skin rashes (7 cases). Immu-

nofluorescent studies showed the presence of IgG in 11/11 patients studied, of C3 in 8/11, of C4 in 2/8 and of C1q in 4/8. Plasma C3 was normal. Plasma C1q, C4 and C3PA were significantly lower than in controls (mean values: 75 vs. 99%, 29 vs. 43 mg/100 ml, 18 vs. 26 mg/100 ml). The immunopathologic findings did not differ significantly from those observed in the apparently isolated MGN.

Uremic neurotoxins. *N. K. Man, G. Cueille, J. Boudet, J. Zingraff, A. Becker, T. Driieke, P. Jungers, A. Sausse and J. L. Funck-Brentano. Département de Néphrologie, Hôpital Necker et Laboratoires de Recherches, Rhône-Poulenc, Paris, France.* Our previous studies have shown a strong correlation between uremic neuropathy and plasma retention of solutes of middle molecular weight range (300 to 2,000 daltons). In order to characterize the solute(s) which might be responsible for uremic neuropathy, plasma samples of healthy subjects ($N = 20$), uncomplicated dialyzed patients ($N = 47$) and patients with progressive neuropathy were analyzed by high performance gel chromatography and then by ion exchange chromatography. Comparison of chromatographic patterns led us to isolate a fraction labeled "b4" which was found in uniquely high concentration in plasma of neuropathic patients. Further, fraction "b4" concentration decreased as the neurologic status of patients improved when they were treated with an adequate dialysis strategy. Amino-acid analysis of this fraction gave 10 to 11 amino acids which correspond to a total mol wt of 1187 to 1289 daltons. Purification of fraction "b4" by thin layer chromatography on silica gel showed the presence of four organic solutes. Only one is of polypeptidic nature. Neurotoxicity of total plasma and chromatographic fractions was tested on isolated sural nerve of *Rana esculenta*. No inhibition of the response to calibrated stimulation was found when the nerve was incubated in normal plasma or in plasma from uncomplicated dialyzed subjects. Total plasma and fraction "b4" from neuropathic patients gave positive results. Our data show new evidence that uremic neuropathy is due to the plasma retention of neurotoxins of 1100 to 1300 mol wt.

Selective bilateral renal-artery embolization (RAE) as treatment of malignant hypertension in two repetitive dialysis patients. *J. J. Merland, J. Rottembourg, A. Jardin, P. Thibault, J. J. Rouby, C. Jacobs, M. Legrain. Service de Néphrologie et Clinique Urologique, Hôpital de la Pitié.Paris, Cedex, France.* Bilateral selective RAE has been performed in two anuric repetitive dialysis patients for whom adequate control of malignant hypertension could not be obtained. The embolization procedure involved the use of the Seldinger technique and material made of gelatine sponge, natural thrombine and in one case polytef (Teflon) fragments. In both patients RAE was followed by long-lasting (one week) lumbo-abdominal pain and febrile reaction. Hyperkalemia (8.7 mEq/liter) occurred during the first hours after RAE in one patient. Such a complication was prevented in the second patient by continuous peritoneal dialysis. In one patient normal blood pressure without drugs was observed one month after RAE. Residual plasma renin activity is 2 ng/ml/hr. In the other patient malignant hypertension persisted, associated with very high renin activity, 120 ng/ml/hr. Subsequent bilateral nephrectomy was immediately efficient on blood pressure. Infarction of the kidneys was total on the left side and partial on the right side. Selective RAE is able in some instances of malignant hypertension to take the place of bilateral nephrectomy. Some complications and incomplete results are to be expected. Evaluation of the usefulness and limitations of the procedure requires more extensive investigations.

Hypertension of long-term hemodialysis patients: Studies with an angiotensin II antagonist (P113). *A. Mimran, S. Shaldon, C. Polito, C. Mion, P. Barjon. Montpellier.* Saralasin (P113) was used to evaluate the role of angiotensin in ten hypertensive dialysis patients (age, 28 to 58 yr) maintained on 3 × weekly hemodialysis for 2 to 45 months. After a 30-min control period, P113 was infused i.v. at a low dose (LDI), 0.52 μg/kg/min for 30 min, followed by a high dose (HDI), 2.35 μg/kg/min for 30 min. Blood pressure (BP) was continuously measured with an arteriosonde. Hematocrit (Hct), plasma Na^+, plasma K^+ and plasma renin activity (PRA) were measured immediately before and at the end of LDI and HDI periods. The study was performed four hours before and repeated one hour after a four-hour hemodialysis (HD). Before HD, control BP was 159 ± 7/104 ± 5 mm Hg (MAP, 123 ± 5), LDI and HD P113 reduced MAP by 15 ± 2 ($P < 0.001$) and 17 ± 3 mm Hg ($P < 0.001$), respectively, and PRA increased from a control of 26 ± 4 to 42 ± 9 (LDI) and 40 ± 9 ng/ml/hr (HDI). HD induced a mean weight loss of 1.4 ± 0.2 kg associated with a MAP fall of 13 ± 3 mm Hg ($P < 0.01$). After HD, saralasin produced a similar fall in MAP and increase in PRA as before HD. The hypotensive effect of P113 suggests that the endogenous angiotensin II pressor effect was responsible in part for the hypertension. The P113 hypotensive effect together with the MAP reduction during HD suggest that hypertension in dialysis patients is maintained by volume and vasoconstrictor factors. However, two patients did not respond to P113 but one had a marked drop in BP with HD alone, suggesting that hypertension may also be totally volume-dependent. P113 may be of clinical value in the assessment of the ultrafiltration requirement for BP control.

Angiotensin receptors in different target organs. *Marie-Gabrielle Pernollet, Marie-Aude Devynck and Philippe Meyer. Physiologie and Pharmacologie, INSERM U7, Hôpital Necker, Paris, France.* Having at our disposition a radioactive angiotensin of high specific activity possessing all the biological activity of the unlabelled hormone has permitted the study of the interaction of the hormone with its specific receptor sites. Such studies have been carried out at the level of different target organs: the rabbit aorta has been taken as a model of vascular smooth muscle, the rat uterus as a model of nonvascular smooth muscle and, finally, the binding of angiotensin II has also been studied in the rat adrenal glands. The properties of the binding sites for angiotensin in these different tissues have been compared—with particular reference to their cellular localization, the kinetic characteristics of the binding and their specificity vis à vis different structural analogues of angiotensin II. Finally, the problem of a possible regulation of the binding capacity of the target cells as a function of levels of circulating hormone has been studied in two of these tissues. After renin suppression by binephrectomy, there appears to be a modification of the binding capacity of isolated membranes of uterus and adrenals. The characteristics of these different binding sites and their behavior after disappearance of the endogenous hormone are analogous to those already described in other quite different hormone-receptor systems.

An experimental model of massive proteinuria in the dog. *J. Sadowski and P. P. Lambert. Queen Elisabeth Medical Foundation, Brussels, Belgium.* A concentrated urea solution (8M) was used by Kefalides and Winzler (1966) to solubilize *in vitro* the renal glomerular basement membrane. In the present study an attempt was made to utilize this property of urea for modification of glomerular permeability *in vivo*. In nine pentobarbital-anesthetized dogs, the left renal artery was clamped at the aorta for five minutes and 10 ml of 4M urea in a 1:1 mixture of plasma and water was injected into the kidney during three minutes. A further two minutes were allowed for urea to remain in contact with kidney tissue before release of the clamp. Simultaneously, a five-minute total renal ischemia was produced in the contralateral control kidney by inflating a catheter baloon appropriately positioned in the aorta. Protein excretion increased from a control of 0.6 ± (SEM) 0.2 to 4.8 ± 1.6 mg/min for the urea-perfused but remained unchanged for the control kidney. Renal clearances of inulin and para-aminohippurate (PAH) of the experimental kidney decreased 24 and 42%, respectively. The extraction ratio of PAH fell 12% on the average. The Sephadex gel filtration and electrophoresis of urinary proteins disclosed a pattern of nonselective glomerular proteinuria. Electron microscopic studies and investigations of glomerular permeability to neutral macromolecules are in course. The developed model of acute unilateral nephrotic-like syndrome enables morphologic and physiopathologic studies of the early stage of massive proteinuria in the dog.

Detection of C1q binding substances in sera of patients with glomerulonephritis. *Alain T. Sobel, Danièle Dechatrette and Gilbert Lagrue. INSERM U 139, Department of Nephrology, Henri-Mondor Hospital, Creteil, France.* Participation of immune complexes and complement in the pathogenesis of a variety of glomerulonephritides has been established. Clq, being the recognition protein of the classical complement system, has proved to be a sensitive detector of immune complexes and other complement-reactive materials in serum. We recently developed the C1q deviation test (*J Exp Med* 142:139, 1975), which quantitates the interference of immune complexes (AgAb) with (^{125}I) C1q binding to sensitized sheep erythrocytes (EA). In a mixture of EA, AgAb and C1q, a proportion of C1q is deviated and bound by the complexes: AgAb + EA + C1q → AgAb C1q + EA C1q + C1q. Separation of cell-bound and fluid phase C1q is accomplished by an original method allowing excellent accuracy and reproducibility. The C1q deviation test is rapid, simple and sensitive. It allows the detection in human serum of 5 μg/ml of gamma-globulin aggregates or BSA-antiBSA complexes; 10 μg/ml of native or single-stranded DNA, 35 μg/ml of certain C1q-reactive endotoxins. One hundred ninety-seven sera from 144 patients were tested. ^{125}I-C1q binding to EA in pathological sera was compared to the binding in normal human serum. A C1q deviation of 15% or more was considered to be a positive result. Sera from patients with AGN, membranous GN, minimal change disease and membranoproliferative GN displayed a C1q deviation in 78%, 46%, 30% and 22% of the cases, respectively. In contrast, positive results were observed in only 12% of the patients with hypertension and 8% of the cases with mesangial IgA deposits. Sera of 17 presumably normal controls were negative, as well as sera from patients with various kidney diseases such as myeloma, renal amyloidosis, gout and lithiasis. Except in AGN cases, the degree of C1q deviation was low. These results suggest that C1q deviation in sera of patients with glomerulonephritis may be due to immune complexes but also to other unknown substances. They emphasize the necessity of isolating and biochemically characterizing C1q-reactive materials in pathological sera.